(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 072 286**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 82401384.1

(22) Date of filing: 27.07.82

(51) Int. Cl.³: **C 07 H 15/18**, C 07 H 15/26, C 07 F 9/09, C 07 F 9/10, C 07 F 9/58, C 07 D 457/06, C 07 D 473/08, C 07 D 213/82, C 07 D 213/81, C 07 C 103/50, C 07 C 103/38

(30) Priority: 03.08.81 IT 4903181

(43) Date of publication of application: 16.02.83 Bulletin 83/7

(84) Designated Contracting States: AT BE CH DE FR GB LI LU NL SE

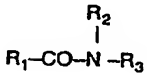
(71) Applicant: FIDIA SpA, Via Ponte Della Fabbrica 3-A, I-35031 Abano Terme (Padova) (IT)

(72) Inventor: Della Valle, Francesco, Via Cerato 14, Padova (IT)
Inventor: Romeo, Aurelio, Viale Ippocrate 93, Rome (IT)

(74) Representative: Hirsch, Marc-Roger, 34 rue de Bassano, F-75008 Paris (FR)

(54) Organic amide compounds derived from nitrogenous lipids.

(57) Organic amide compounds of the formula:



wherein:

R_1–CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,

R_1 is a hydrogen atom, a C_{1-7} alkyl group, or a C_{4-7} cycloalkyl group, and

R_{3-N} is a residue of a nitrogenous lipid.

The compounds are useful in increasing or stimulating the in vivo biological activity of in vitro biologically active carboxylic acids.

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ORGANIC AMIDE COMPOUNDS DERIVED FROM NITROGENOUS LIPIDS

The present invention relates to novel organic amide compounds, procedures for preparing the compounds, pharmaceutical compositions containing the same and methods for using the compounds. These novel organic amides are primarily comprised of a carboxylic acid moiety and a nitrogenous lipid moiety.

Numerous compounds are known to be active *in vitro* and yet exhibit little or no activity *in vivo*. In particular, numerous carboxylic acids are known to be important in the actions of the peripheral and central nervous systems and are active *in vitro* but are either non-active or only slightly active *in vivo*. Gamma-aminobutyric acid (GABA), for example, is known to be active on the central nervous system *in vitro* and has been suggested as a possible inhibitory transmittor [Louis S. Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics, 4th Ed., p. 429 (1970)]. However, GABA has been found to be ineffective when administered *in vivo* as measured by convulsion tests in mice.

The present inventors have found that compounds of the formula (I), prepared by combining a carboxylic acid, such as GABA, with a nitrogenous lipid, such as a phospholipid or sphingosine, provide amide compounds which are active *in vivo* exhibiting activities far superior to that of the corresponding carboxylic acid or lipid compounds administered alone. For example, the amide of GABA with a sphingosine provides a compound which is far more active *in vivo* than is GABA alone. Similarly, lysergic acid, dihydrolysergic acid and isolysergic acid are essentially inactive when administered alone, but when combined with a sphingosine provide compounds of the formula (I) which have significant *in vivo* activity as measured by hypoprolactinemic effects in rats.

The significantly improved pharmacological properties of the compounds of formula (I) are thought to result from the ability of these compounds to penetrate the hematoencephalic barrier and/or reach the peripheral organs far better than the carboxylic acid compounds alone.

This ability of the compounds of the present invention favors the interaction between the biologically active compound, such as the carboxylic acid, and the situs of the specific interactions present in the membranes.

Hence, the compounds of the present invention are useful for enhancing or increasing the *in vivo* biological activity of *in vitro* biologically active carboxylic acids as well as stimulating the *in vivo* biological activity of *in vitro* biologically active carboxylic acids which have little or no *in vivo* activity.

The novel organic amide compounds of the present invention are represented by the formula (I):

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3 \qquad (I)$$

wherein:

R_1-CO is a residue of an organic carboxylic acid which has a pharmaceutical or biological activity with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,

R_2 is a hydrogen atom or one of a group of hydrocarbons, and

NR_3 is a residue derived from a nitrogenous lipid.

Natural fatty acids normally bound to nitrogen in nitrogenous lipids are described in, for example: Wiegandt, Adv. in Lipid Res., Vol. 9, pp.249-288, Ed. by Paoletti and Kritchezsky (Academic Press, 1971), and Ansell and Hawthorne, Phospholipids, Biochem. Biophys. Acta. Library, Vol. 3, pp.420-425 (Elsevier Pub. Co., 1964).

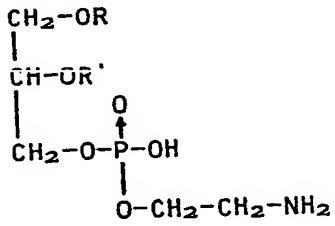
The R_1-COOH acids which give rise to the R_1-CO residue are primarily those acids which are fundamentally important to the peripheral and central nervous systems, such as lysergic, isolysergic, dihydrolysergic, 2-bromo-lysergic, 2-bromo-dihydrolysergic, 1-methyllysergic, 1-methyldihydrolysergic, 1-methyl-2-bromo-lysergic, 1-methyl-2-bromo-dihydrolysergic, gamma-amino-butyric, valproic (2-propylpentanoic), trimethoxybenzoic, nicotinic, isonicotinic, picolinic and theophyllineacetic acids. These acids have the common pharmaceutical characteristic of being active *in vitro* but non-active or only slightly active *in vivo*.

R_2 may be a hydrogen atom or a hydrocarbon, especially a saturated aliphatic hydrocarbon or a saturated cycloaliphatic hydrocarbon group; for example an alkyl having from 1 to 7 carbon atoms such as butyl, isobutyl, tertiarybutyl, propyl, isopropyl, ethyl, and methyl or a cycloalkyl having from 4 to 7 carbon atoms, such as cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The -N-R_3 residue is derived from a nitrogenous lipid, especially from phospholipids and sphingolipids. Phospholipids, natural products that can be extracted from bovine brain tissue, are chemically derived from L-α-glycerophosphoric acid.

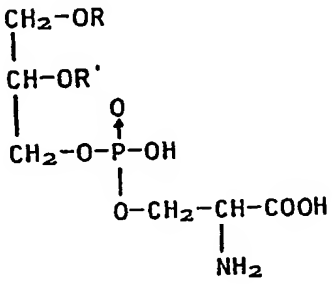
[Lees, M. B., Met. Enzymol, Vol. 3, pp. 328-345 (1957);
Bigon et al, G. Brit. J. Pharmacol., Vol. 67, pp. 611-619 (1979);
Spanner, Form and Function of Phospholipids, Ed. By Ansell et al,
Biochem. Biophys. Acta. Library, Vol. 3, pp. 43-65 (1973)].

The two major phospholipid groups which are utilized are the phosphatidylethanolamines (II) and the phosphatidylserines (III) represented by the following structures:



(II)

and



(III)

wherein:

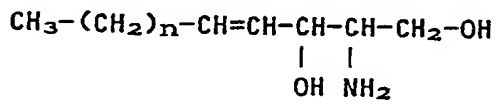
R and R' represent a hydrogen atom or the residue of an organic carboxylic acid, especially, the residue of a saturated or unsaturated fatty acid.

Sphingolipids are natural products extracted, in particular, from animals and vegetables and contain an amino-alcohol moiety [Dawson, Form and Function of Phospholipids, Ed. by Ansell et al, Biochem. Biophys. Acta. Library, Vol. 3, pp. 104-105 (1973); Kaller, Biochem. Zeitschrift, Vol. 334, pp. 451-456 (1961); Sweeley et al, J. Lipid, Res., Vol. 1, pp. 40-47 (1959); Radin, Lipids, Vol. 9, pp. 358-360 (1970].

Especially preferred sphingosines are those having an average of 12 to 22 carbon atoms.

The sphingolipid derivatives which permit the preparation of the compounds (I) of the present invention contain a sphingosinic residue and contain a free sphingosine $-NH_2$ group. Principally these are:

- Sphingosine represented by the formula:

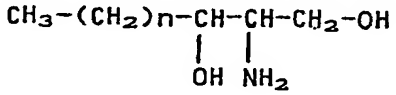


(IV)

wherein:

n may be from 6 to 16.

- Dihydrosphingosine represented by the formula:

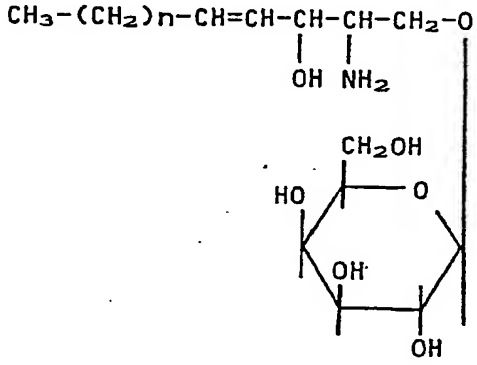


(V)

wherein:

n may be from 8 to 18.

- Psychosine or galactosylsphingosine represented by the formula:

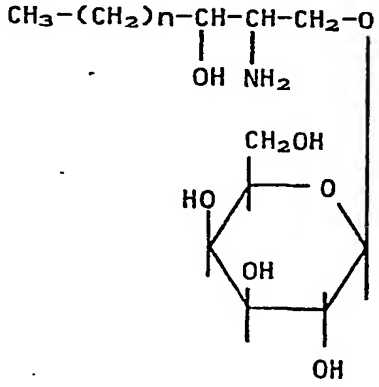


(VI)

wherein:

n may be from 6 to 16.

- Dihydropsychosine represented by the formula:

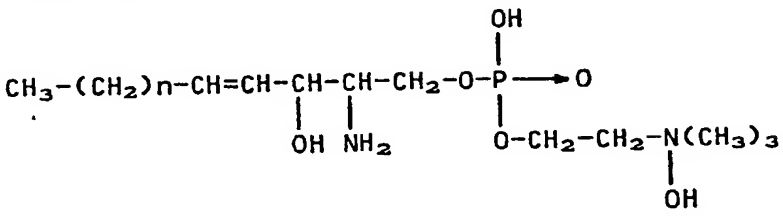


(VII)

wherein:

n may be from 8 to 18.

- Phosphorylcholine sphingosine or lisosphingomyelins represented by the formula:

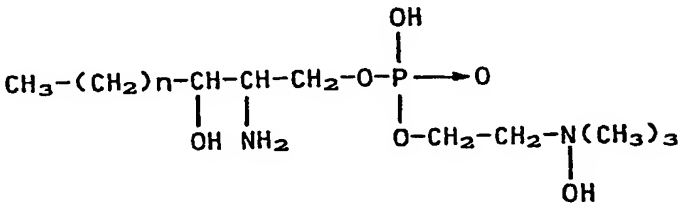


(VIII)

wherein:

n may be from 6 to 16.

- Phosphorylcholine - dihydrosphingosine, or lisodihydrosphingomyelins represented by the formula:

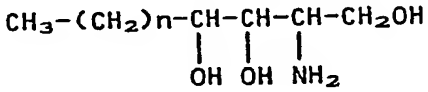


(IX)

wherein:

n may be from 8 to 18.

- Phytosphingosine represented by the formula:

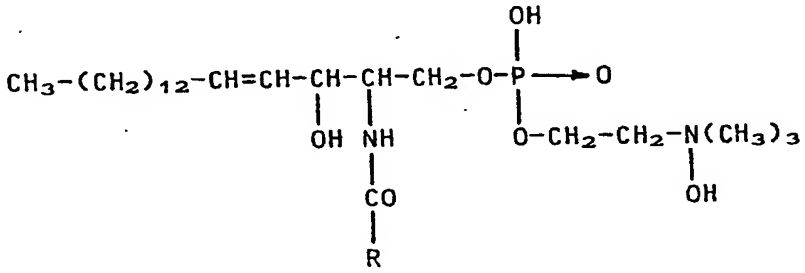


(X)

wherein:

n may be from 11 to 15,

and all other sphingolipids which through hydrolysis are capable of releasing an amine ($-NH_2$) group, such as is indicated below by the sphingomyelin formula (XI):



(XI)

• Preparation Procedures —

The organic amides (I) according to the present invention can be prepared according to a variety of preparation methods in conditions which prevent the esterification of the free oxyhydric acid. Of all the methods which have proved to be particularly appropriate, the following are most preferred:

1. The reaction between the R_1CON_3 azides (corresponding to the R_1-COOH acid) and the nitrogenous lipidic derivatives. The preparation of the R_1CON_3 azides can be realized by utilizing one of the known methods.

2. The acylimidazole preparation method comprising reacting the R_1COOH acid with N, N'-carboxyldiimidazol, followed by the reaction of the thus produced acylimidazole with the nitrogenous lipid.

3. The mixed anhydride preparation method comprising reacting the R_1COOH acid and trifluoracetic acid to form a mixed anhydride and then reacting the mixed anhydride with the nitrogenous lipid.

4. Preparing the chloride of the R_1COOH acid followed by reacting the chloride with the nitrogenous lipid.

5. Direct reaction between the R_1COOH acid and the nitrogenous lipid in the presence of a carbodiimide (for example dicyclohexylcarbodiimide, benzylisopropylcarbodiimide or benzylethylcarbodiimide) or another substance similar to 1-hydroxybenzotriazol.

6. Direct condensation from heating the R_1COOH acid with the nitrogenous lipidic derivatives.

7. Direct reaction between the methyl ester of the R_1COOH acid and the nitrogenous lipidic derivative; this reaction is favored by heating.

8. Preparation of an ester by the reaction between an R_1COOH acid and a phenol (for example, paranitrophenol) followed by the reaction of the ester with the nitrogenous lipid. The ester preparation between the acid and a phenol can be realized by using one of the known methods.

In the preparation of the products described in formula (I) derived from gamma-aminobutyric acid, the method preferably used is that consisting of the initial preparation of a gamma-aminobutyric derivative where the amine group is attached to a protective group, as for example, a phthaloyl or benzyloxycarbonyl group. The derivative thus prepared is then further condensed with the nitrogenous lipid using one of the reactions previously described. The protective group is then eliminated by means of an appropriate reaction and the product (I) is thus obtained. For example, if the protective group is phthaloyl, this group could be eliminated by hydrazinalysis.

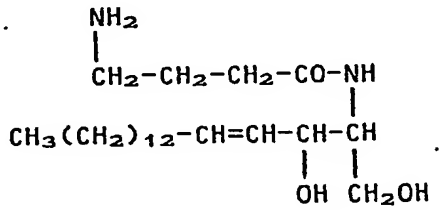
The compounds of formula (I), wherein the R_1-COOH acid contains a basic group (for example, gamma-aminobutyric, nicotinic, lysergic or dihydrolysergic acid), can be salified with therapeutically used acids such as: hydrochloric, hydrobromic, methanesulphonic and malic acids.

As described above, according to the present invention, numerous compounds, particularly carboxylic acids, can be combined with nitrogenous lipids to produce amide compounds which are pharmaceutically active *in vivo* Although not limiting, the following examples illustrate the products, preparation procedures and pharmaceutical preparations of the present invention.

EXAMPLE 1

• Product 1

Gamma-aminobutyrylsphingosine amides of the formula:



a — A gamma-phthalmid-butyryl-sphingosine-amide (Product 1a) is prepared as follows: 5.7g de sphingosine (obtained from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 50 ml of absolute ethanol. 8.9g of the para-nitrophenylester of the gamma-phthalmid-butyril-sphingosine acid (prepared according to: J. Org. Chem. 27, 684-696, 1962)are added to the solution.

The solution is then heated and left to precipitate for 2 hours and the solvent is vacuum separated. The residue is mixed with 500 ml of a methylene chloride ethanol mixture (4/1). The organic solution is washed

with an aqueous solution of sodium carbonate and then with water. The organic solution is dried on sodium sulphate, filtered and the solvent is then vacuum separated.

The residue crystallizes from methylene chloride - n-hexane, M.P. 97°C, yield 7.3g.

_ Thin layer chromatography (silica gel) using a eluent mixture of methylene chloride / ethyl acetate/methanol (70/30/10), indicates that it is a single compound with Rf of 0.4.

_ Elementary analysis gives the following results (%) —

— C 70.20; H 8.94; N 5.61

For $C_{30}H_{46}N_2O_4$, theoretical % calculated is — C 70.00; H 9.01; N 5.44

b — 5.14g of the gamma-phthalamid-butyryl sphingosine-amide (Product 1a) are treated with 30 ml of absolute ethanol; 20 ml of an ethanolic solution of 1 Molar hydrazine are added and heated and allowed to precipitate for 2 hrs. The solvent is then evaporated in a vacuum and 50 ml of acetic acid (2 Normal) is added to the residue and heated for 10 minutes at 50°C. The mixture is left to cool to room temperature and filtered. The filtered solution is concentrated in vacuum and a water solution of NaOH (2N) until a clearly alkaline pH is obtained.

The aqueous phase is extracted with a mixture of methylene chloride/ethanol (4/1). The organic solution is dried on sodium sulphate, which is filtered and evaporated. The residue crystallizes from tertiarybutyl-methyl ether, and gamma-amino-butyryl-sphingosine amides (Product 1) M.P. 87°C, are thus obtained (yield 3.1g).

_ Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/water/ammonia concentrated aqueous solution (70/35/5/1) indicates that the Product 1 is a single compound with Rf of 0.16.

_ Elementary analysis gives the following results (%) —

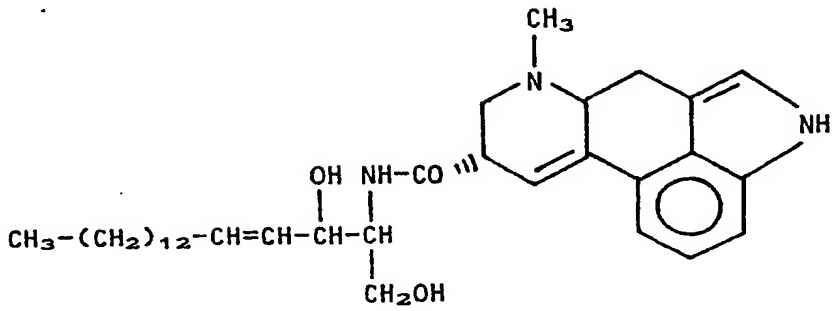
— C 68.56; H 11.50; N 7.37

For $C_{22}H_{44}N_2O_3$, theoretical % calculated is — C 68.70; H 11.53; N 7.28

EXAMPLE 2

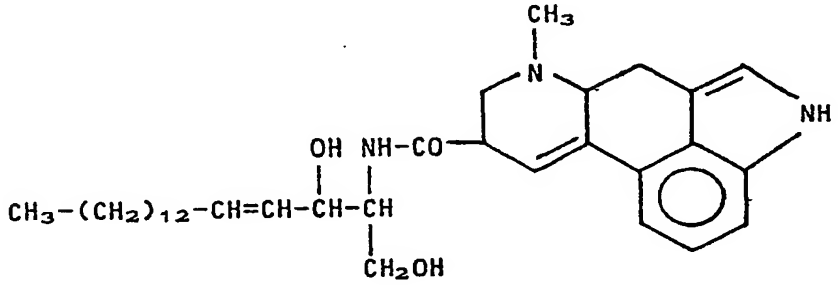
• Products 2.1 and 2.2

Isolisergylsphingosine amides of the formula:



(Product 2.1)

and lysergylsphingosine amides, an isomer from the formula (2.1), of the formula:



(Product 2.2)

6.7g of D-lysergic acid are treated with 400 ml of dimethylformamide (DMF) (this reaction is conducted taking care to work away from light); the lysergic acid gradually forms a solution. 4.45g of N,N'-carbonyl diimidazole dissolved in 125 ml of DMF are added to the solution and kept at room temperature for 2 hours. 8.25g of sphingosine (obtained from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are added and the mixture is maintained at room temperature for 24 hours.

DMF is evaporated in vacuum and the residue is treated with 1000 ml of ethyl acetate, the suspension is filtered and the organic solution washed with 5M of ammonia and then with water. The organic solution is dried on sodium sulphate, and then filtered and evaporated, thus obtaining a residue.

The residue is then chromatographically fractionated separating the two compounds: Product 2.1; Product 2.2.

a — Product 2.1-Isolysergylsphingosine-amide

– Chromatography on silica gel plates using an eluent mixture of ethyl acetate/methanol (80/20), indicates that it is a single compound with Rf 0.74.

Evaluation of the specific rotating power is carried out in methanol solution (1% using a 1 dm polarimetric tube — result is $(\alpha)_D$ = +235°.

– Elementary analysis gives the following results (%) —

— C 74.16; H 9.55; N 7.78

For $C_{34}H_{51}N_3O_3$, theoretical % calculated is — C 74.27; H 9.35; N 7.64

b — Product 2.2-Lysergylsphingosine-amide

(crystallizes from acetone, M.P. 139°C).

– Chromatography on silica gel plates using an eluent mixture of ethyl mixture of ethyl acetate/methanol (80/20), indicates that it is a single compound with Rf 0.30.

Evaluation of a specific rotary power is carried out in 1% chloroform using a 1 dm polarimetric tube — result is $(\alpha)_D$ = +3.

– Elementary analysis gives the following results (%) —

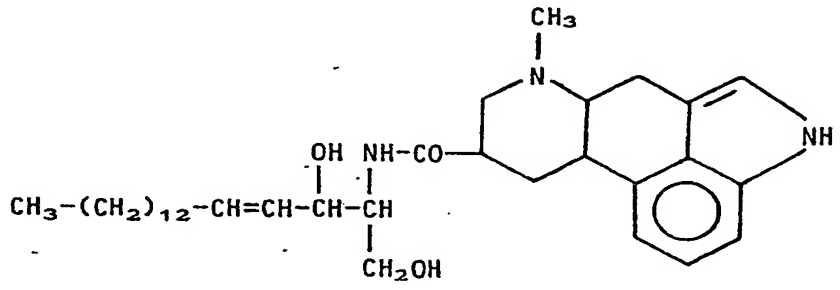
— C 74.10; H 9.42; N 7.80

For $C_{34}H_{51}N_3O_3$, theoretical % calculated is — C 74.27; H 9.35; N 7.64

EXAMPLE 3

• Product 3

a — Dihydrolysergylsphingosine amide of the formula:



2.7g of dihydrolysergic acid (prepared from catalytic hydrogenation of the lysergic acid) and 2.7g of 1-hydroxybenzotriazole are added to 100 ml of chloroform. The mixture, under continual agitation, is brought to 30°C, after which 3g of sphingosine (obtained from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) and 2g of dicyclohexylcarbodiimide are added.

The mixture is heated and allowed to precipitate for 1 hour, brought to room temperature and then 25 ml of ethanol are added.

The organic solution is washed with 5M ammonia and then with water. The organic solution is vacuum dried, thus obtaining a residue and solubilized in 30 ml of methanol.

The methanolic solution is brought to 0° thus precipitating the dicyclohexylurea; the suspension is filtered and the solvent is eliminated from the filtered substance by vacuum. The residue is solubilized by heating with 45 ml of acetone. While cooling, the dihydrolysergylsphingosine amides crystallize, M.P. 206°C, yield 3.8g.

- Thin layer chromatography (silica gel) using an eluent mixture of methylene chloride/ethyl acetate/methanol (60/30/15), indicates that it is a single compound with Rf of 0.25.

Evaluation of a specific rotaty power is carried out in a 2% methanol solution using a 1 dm polarimetric tube — result is $(\alpha)_D = -63°$.

- Elementary analysis gives the following results (%) —

— C 73.85; H 9.72; N 7.34

For $C_{34}H_{53}N_3O_3$, theoretical % calculated is — C 74.00; H 9.68; N 7.26.

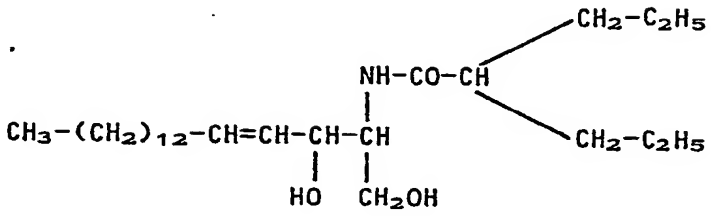
b — The preparation of the salt with methane sulphonic acid from the dihydrolysergyl sphingosine amide is as follows: 1g of dihydrolysergyl sphingosine amide is dissolved in 50 ml of acetone, 0,18g of methane sulphonic acid are added. The solution is then concentrated in small volumes crystallizing the salt of the dihydrolysergylsphingosine amides with methane sulphonic acid.

Evaluation of a specific rotary power is carried out in a methanol solution of 2% using a 1 dm polarimetric tube — result is $(\alpha)_D = -41.5°$.

EXAMPLE 4

• Product 4

Valproylsphingosine amide of the formula:



11.5g of sphingosine (taken from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 1000 ml of absolute ethanol. To this solution 13.1g of the para-nitrophenylester of valproic acid [prepared according to: Chim. Ther. 3, (5), 336-42, (1968)] is added.

This solution is then treated as for that described in Example 5. The residue is crystallized by tertiarybutyl methyl ether, M.P. 118°C, yield 14.9g.

– Thin layer chromatography (silica gel) utilizing an eluent mixture formed from: methylene chloride/ethyl acetate/methanol (70/30/10), indicates that it is a single compound with Rf 0.85.

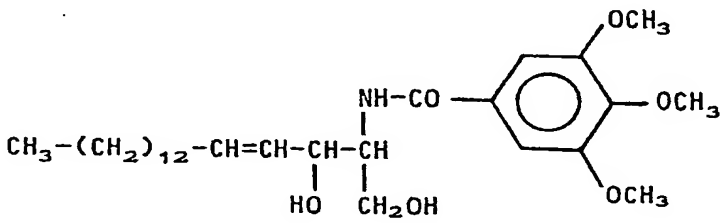
– Elementary analysis gives the following results (%) –

–	C	73.30;	H	12.25;	N 3.11
For $C_{26}H_{51}NO_3$, theoretical % calculated is –	C	73.36;	H	12.08;	N 3.29

EXAMPLE 5

• Product 5

3,4,5-Trimethoxy-benzoylsphingosine amide of the formula:



5g of sphingosine (taken from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 500 ml of absolute ethanol. To this solution 7.35g of a p-nitrophenyl-ester of the 3,4,5-trimethoxybenzoyl acid are added [prepared according to: Anales Asoc. Guim. Argentina 26, 51-56, (1938)].
This mixture is heated and left to precipitate for 2 hours and the solvent is vacuum separated. The residue is mixed with 500 ml of a methylene chloride/ethanol mixture (4/1). The organic solution is washed with an aqueous solution of sodium carbonate and then with water. The organic solution is dried on sodium sulphate, filtered and the solvent is then vacuum separated. The residue crystallizes from tertiarylbutyl methyl ether, M.P. 130°C, yield 7.3g.

- Thin layer chromatography (silica gel) using an eluent mixture formed by methylene chloride/ethyl acetate/methanol (40/30/10), indicates that it is a single compound with Rf of 0.5.

- Elementary analysis givesthe following results (%) —

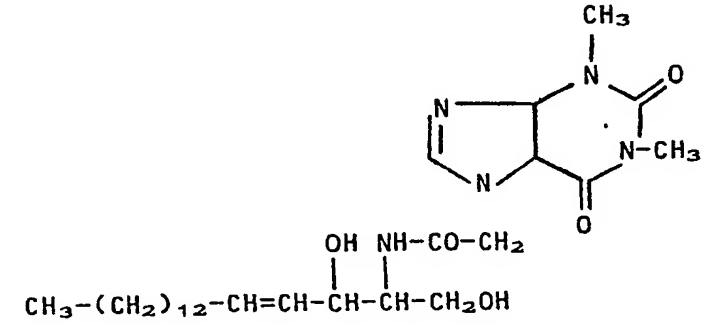
— C 68.01; H 9.78; N 2.67

For $C_{28}H_{47}NO_6$, theoretical % calculated is — C 68.12; H 9.60; N 2.84

EXAMPLE 6

• Product 6

Theophyllinacetylsphingosine amide of the formula:



6g of sphingosine (taken from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 500 ml of absolute ethanol. To this solution are added 9.5g of a p-nitro-phenylester of theophyllineacetic acid [prepared according to: Annalen (1976) 860-75]. The same procedure as described in Example 5 is then followed.

The residue crystallizes from methanol, M.P. 189°C, yield 8.5g.

- Thin layer chromatography (silica gel) using an eluent mixture formed by methylene chloride/ethyl acetate/methanol (60/30/20), indicates that it is a single compound with Rf of 0.6.

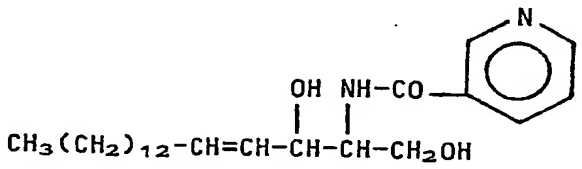
- Elementary analysis gives the following results (%) -

	- C	62.31;	H	8.70;	N 13.30
For $C_{27}H_{45}N_5O_5$, theoretical % calculated is - C	62.40;	H	8.73;	N	13.48

EXAMPLE 7

• Product 7

Nicotinylsphingosine amide of the formula:



5g of sphingosine (obtained from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 500 ml of absolute ethanol. 5.5g of p-nitrophenylester of the nicotinic acid are added to the solution [prepared according to: J. Chem. Soc. B. (1971) 2401-6]. The same procedure as described in Example 5 is then followed.

The residue crystallizes from tertiarybutyl methyl ether, M.P. 105°C, yield 6.7g.

Thin layer chromatography (silica gel) using an eluent mixture formed by methylene chloride/ethyl acetate/methanol (70/30/10) indicates that it is a single compound with an Rf of 0.23.

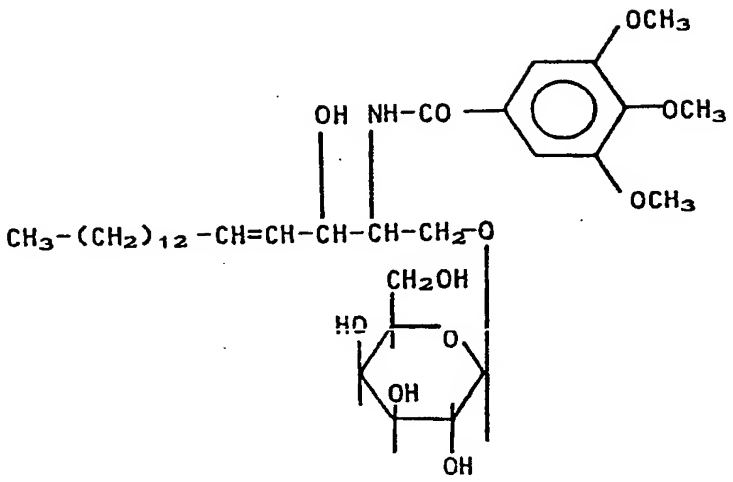
Elementary analysis gives the following results (%) -

	- C	71.12;	H	9.78;	N 6.70
For $C_{24}H_{40}N_2O_2$, theoretical % calculated is - C	71.24;	H	9.97;	N	6.92

EXAMPLE 8

• Product 8

3,4,5-Trimethoxybenzoylpsycosine amide of the formula:



5g of psycosine (taken from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 4.8g of the p-nitrophenylester of trimethoxybenzoylpsycosine acid in an ethanolic solution (see Example 5). The same procedure as described in Example 5 is then followed.

The residue crystallizes from ethanol - acetone, M.P. 135°C, yield 6.7g.

– Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/water (110/40/6), indicates that it is a single compound with Rf of 0.85.

– Elementary analysis gives the following results (%) –

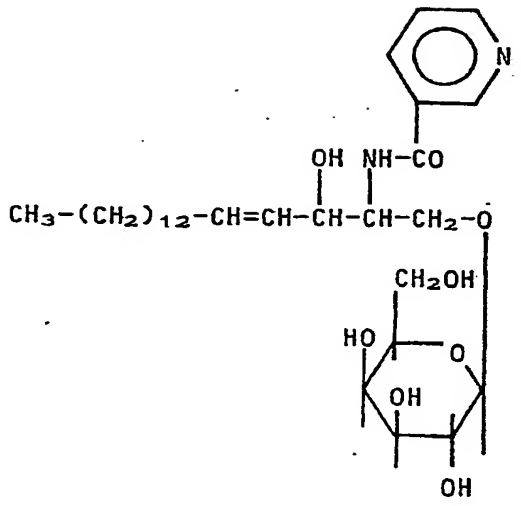
– C 62.02; H 8.54; N 1.99

For $C_{34}H_{57}NO_{11}$, theoretical % calculated is – C 62.27; H 8.76; N 2.14

EXAMPLE 9

• Product 9

Nicotinylpsycosine amide of the formula:



5g of psycosine (obtained from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 3.5g of the p-nitrophenylester of nicotinic acid in an ethanolic solution (see Example 7). The same procedure as described in Example 5 is then followed.

The residue crystallizes from acetone, M.P. 140°C, yield 6.7g.

– Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/water (110/40/6), indicates that it is a single compound with an Rf of 0.80.

– Elementary analysis gives the following results (%) –

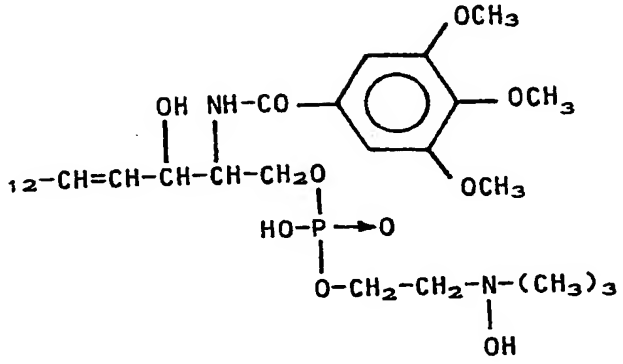
– C 63.30; H 8.75; N 4.80

For $C_{30}H_{50}N_2O_8$, theoretical % calculated is – C 63.58; H 8.80; N 4.94

EXAMPLE 10

• Product 10

3,4,5-Trimethoxybenzoyl-sphingosinephosphorylcholine amide of the formula:



5g of sphingosinephosphorylcholine (taken from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 4.6g of a p-nitrophenylester of the 3,4,5-trimethoxybenzoic acid in an ethanolic solution (see Example 5).

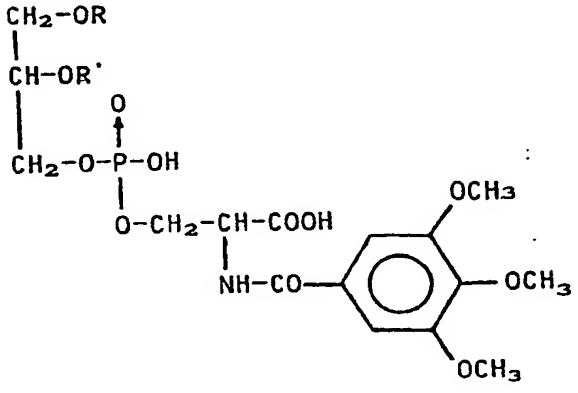
The same procedure as described in Example 5 is then followed. The residue crystallizes from tertiarybutyl methyl ether, M.P. 127°C, yield 6.1g.

Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/water (60/35/8), indicates that it is a single compound with a Rf of 0.25.

EXAMPLE 11

• Product 11

3,4,5-Trimethoxybenzoyl-phosphatidylserine amide of the formula:



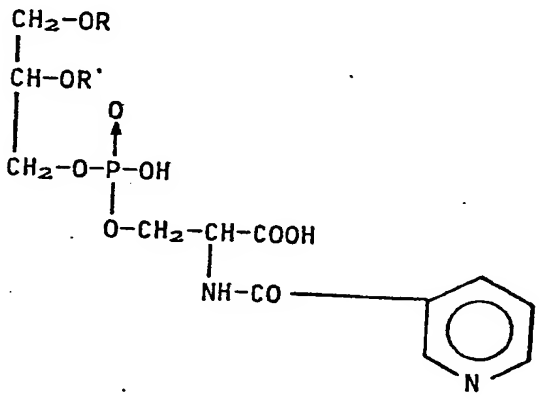
5g of phosphatidylserine (taken from the phospholipids present in the bovine brain and in which the groups R and R' are mainly stearic, palmitic, oleic, linolenic, linoleic and arachidonic acid residues) are treated with 2.8g of a p-nitrophenylester of 3,4,5-trimethoxybenzoyl acid in an ethanolic solution (see Example 5). The same procedure as described in Example 5 is then followed, excluding the wash of the organic solution with Na_2CO_3. The residue is purified by chromatography, yield 4.5g.

- Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/water (70/30/5), indicates that it is a single compound with an Rf of 0.5.

EXAMPLE 12

• Product 12

Nicotinylphosphatidylserine amide of the formula:



5g of phosphatidylserine (taken from the phospholipids present in the bovine brain and in which the groups R and R' are mainly stearic, palmitic, oleic, linolenic, linoleic and arachidonic acid residues) are treated with 2g of a p-nitrophenylester of nicotinic acid in an ethanolic solution (see Example 7).

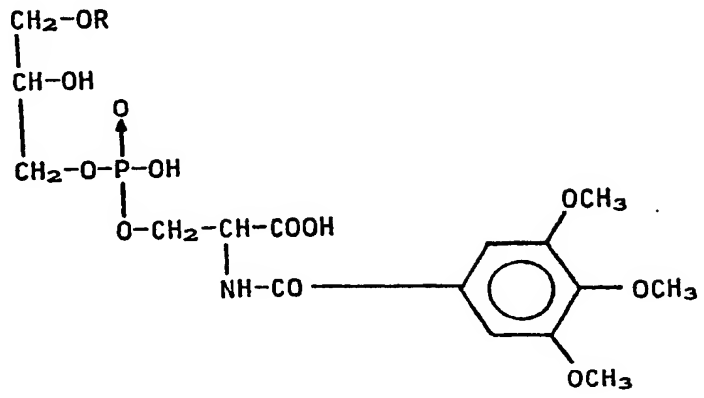
The same procedure as described in Example 5 is then followed, excluding the wash of the organic solution with Na_2CO_3. The residue is purified by chromatography, yield 5.1g.

- Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/water (70/35/5), indicates that it is a single compound with an Rf of 0.5.

EXAMPLE 13

• Product 13

3,4,5-Trimethoxybenzoyl-isophosphatidylserine amide of the formula:



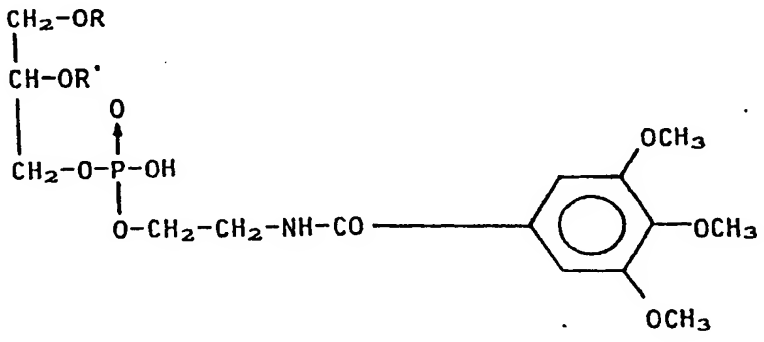
5g of lisophosphtidylserine (taken from the enzymatic hydrolysis of phosphatidylserine, the R group in the lisophosphatidylserine being mainly stearic or oleic acid) are treated with 4.3g of a p-nitrophenyl-ester of 3,4,5-trimethoxybenzoyl acid in an ethanolic solution (see Example 5). The same procedure as described in Example 5 is then followed, excluding the wash of the organic solution with Na_2CO_3.
The residue is purified by chromatography, yield 6.0g.

Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/water (60/35/8), indicates that it is a single compound with an Rf of 0.3.

EXAMPLE 14

• Product 14

3,4,5-Trimethoxybenzoylphosphatidylethanolamine amide of the formula:



5g of phosphatidylethanolamine (taken from the phospholipids present in the bovine brain and in which the groups R and R' are mainly oleic, stearic, palmitic, linoleic and arachidonic acid residues) are treated with 3g of a p-nitrophenylester of 3,4,5-trimethoxybenzoyl acid in an ethanolic solution (see Example 5). The same procedure as described in Example 5 is then followed.

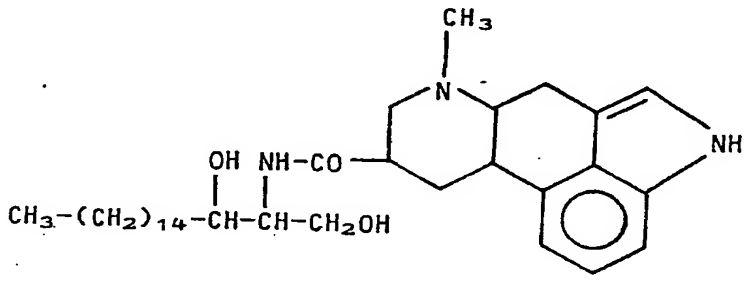
The residue is purified by chromatography, yield 5.1g.

– Thin layer chromatography (silica gel) using an eluent mixture formed by methylene chlorine/ethyl acetate/methanol (70/30/20), indicates that it is a single compound with an Rf of 0.30.

EXAMPLE 15

• Product 15

Dihydrolysergyldihydrosphingosine amide of the formula:



The procedure is carried out as described in Example 3, beginning with 2.5g of dihydrosphingosine (obtained through the catalytical hydrogenation of the sphingosine C_{18}); 2.24g of dihydrolysergic acid; 2.24g of 1-hydroxybenzotriazol; and 2.06g of dicyclohexyl-carbodiimide.

The reaction takes place in chloroform (130 ml).

The compound crystallizes from acetone, M.P. 200°C, yield 3.6g.

– Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/ammonia 1N (64/24/3.2), indicates that it is a single compound with an Rf of 0.69.

Evaluation of the specific rotary power is carried out in a 2% methanol solution using a 1 dm polarimetric tube. Results: $(\alpha)_D = -47.5°$.

– Elementary analysis gives the following results (%) –

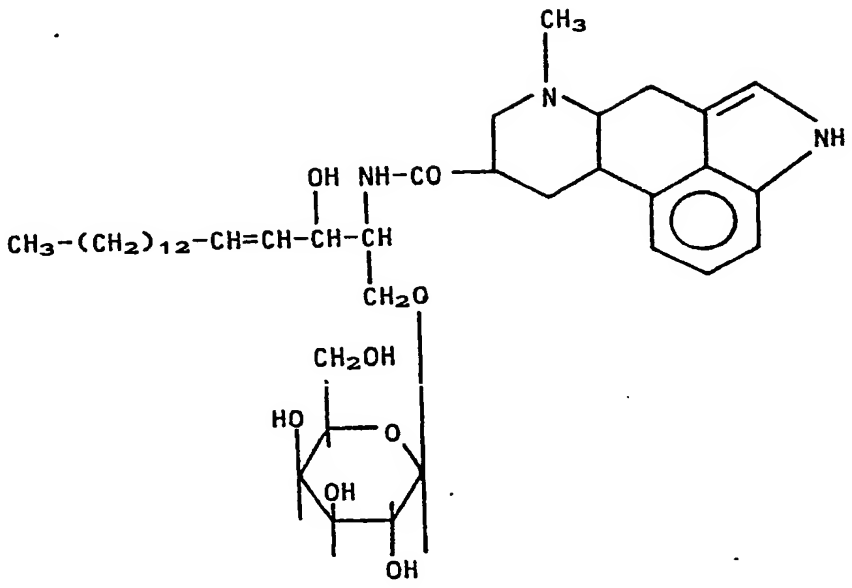
– C 73.61; H 10.22; N 7.45

For $C_{34}H_{55}N_3O_3$, theoretical % calculated is – C 73.73; H 10.01; N 7.59

EXAMPLE 16

• Product 16

Dihydrolysergylpsychosine amide of the formula:



The procedure is carried out as described in Example 3, beginning with 2.8g of psychosine (obtained from the sphingolipids present in the bovine brain and containing a sphingosinic residue C_{18}); 1.62g of dihydrolysergic acid; 1.62g of 1-hydroxybenzotriazol; and 2.06g of dicyclohexylcarbodiimide. The reaction takes place in a chloroform solution, 100 ml of chloroform.

The compound crystallizes from ethyl acetate, M.P. 140°C, yield 3.8g.

_ Thin layer chromatography (silica gel) using an eluent mixture formed by chloroform/methanol/ammonia 1N (64/24/3.2), indicates that it is a single compound with an Rf of 0.43.

Evaluation of the specific rotary power is carried out in a 2% methanol solution using a 1 dm polarimetric tube. Results: $(\alpha)_D = -32°$.

_ Elementary analysis gives the following results (%) —

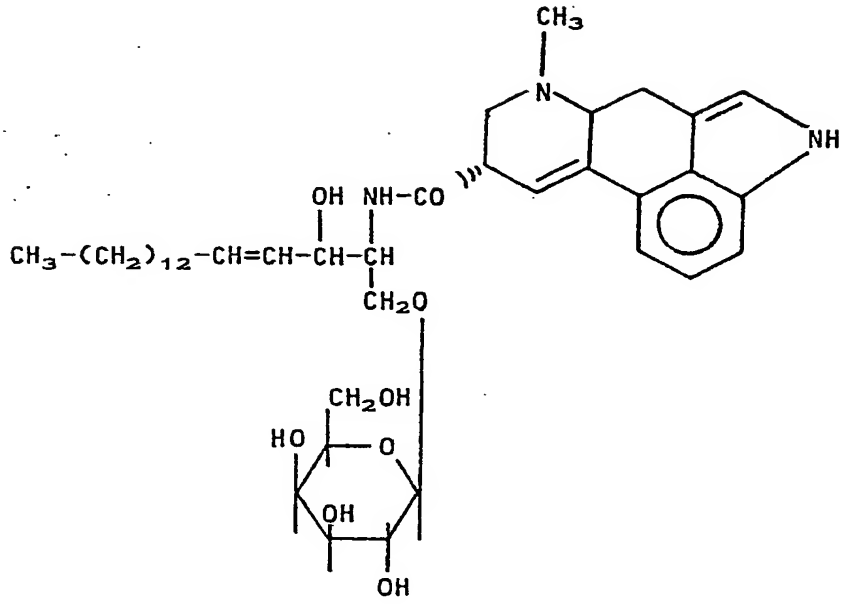
— C 67.01; H 8.62; N 5.48

For $C_{40}H_{63}N_3O_8$, theoretical % calculated is — C 67.29; H 8.89; N 5.89

EXAMPLE 17

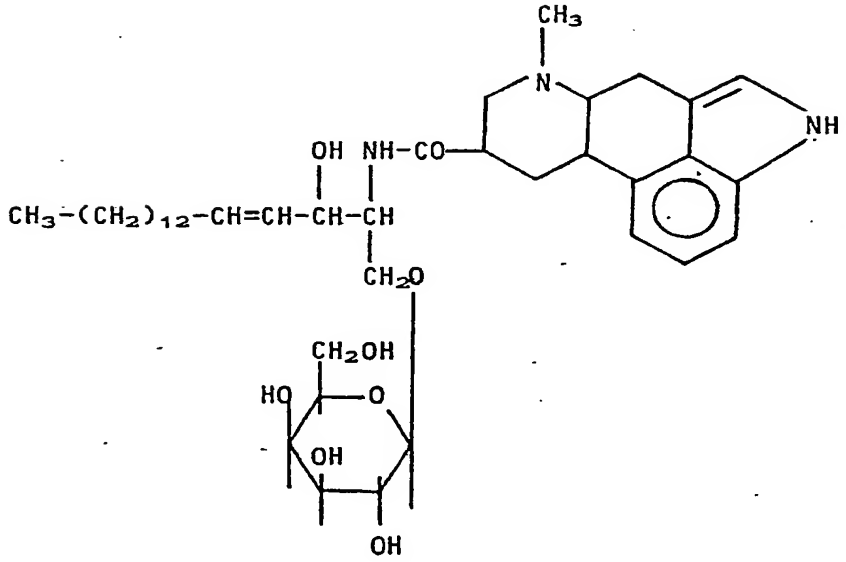
• Products 17.1 and 17.2

Isolysergylpsychosine amide of the formula:



(Product 17.1)

and lysergylpsychosine amide of the formula:



(Product 17.2)

The procedure is carried out as described in Example 2, beginning with 6.7g of D-lysergic acid; 4.45g of N-N'-carbonyldiimidazol, 12.7g of psychosine (taken from sphingolipids present in the bovine brain and containing a sphingosinic residue C_{18}). The reaction takes place in a dimethylformamide solution of the same volume as described in Example 2. The residue is then chromatographically fractionated separating the two compounds: Product 17.1 and Product 17.2.

a — Product 17.1 — isolysergyl psychosine amide, M.P. 97°-100°C.

– Chromatography on silica gel using an eluent mixture formed by chloroform/methanol/ammonia 1M (64/24/3.2), indicates that it is a single compound with Rf 0.76.

Evaluation of the specific rotary power is carried out in a 2% methanol solution using a 1 dm polarimetric tube. Results: $(\alpha)_D = +143°$.

– Elementary analysis gives the following results (%) —

— C 67.35; H 8.51; N 5.65

For $C_{40}H_{61}N_3O_8$, theoretical % calculated is — C 67.48; H 8.64; N 5.90

b — Product 17.2 — lysergylpsychosine amide, M.P. 122°-126°C.

– Chromatography on silica gel using an eluent mixed formed by chloroform/methanol/ammonia 1M (64/24/3.2), indicates that it is a single compound with an Rf of 0.59.

Evaluation of the specific rotary power is carried out in a 2% methanol solution using a 1 dm polarimetric tube. Results: $(\alpha)_D = +2°$.

– Elementary analysis gives the following results (%) —

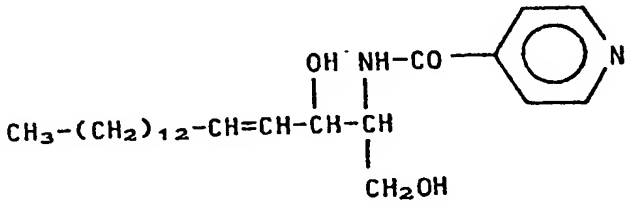
— C 67.40; H 8.56; N 5.71

For $C_{40}H_{61}N_3O_8$, theoretical % calculated is — C 67.48; H 8.64; N 5.90

EXAMPLE 18

• Product 18

Isonicotinylsphingosine amide of the formula:



5g of sphingosine (taken from the sphingolipids present in the bovine brain and corresponding to a sphingosine C_{18}) are treated with 500 ml absolute ethanol. To the solution, 5.5g of the p-nitrophenylester of isonicotinic acid [prepared according to: C.A. 59, 8708b (1963)] is added. The same procedure as described in Example 5 is then followed. The residue crystallizes from acetonitrile, M.P. 116°C, yield 6.0g.

- Thin layer chromatography (silica gel) using an eluent mixture formed by methylene chloride/ethyl acetate/methanol (70/30/15), indicates that it is a single compound with an Rf of 0.49.

- Elementary analysis gives the following results (%) -

-	C 71.12;	H 9.78;	N 6.70
For $C_{24}H_{40}N_2O_3$, theoretical % calculated is -	C 71.24;	H 9.97;	N 6.92

PHARMACOLOGICAL PROPERTIES

The compounds described above in Examples 1, 2, 3, 15 and 16 were tested for pharmacological activity. These compounds were tested both *in vitro* and *in vivo* in laboratory animals and proved to be capable of acting directly on the central nervous system.

Product 1 of Example 1 - Gamma-aminobutyrylsphingosine amide -

a. in vitro tests:

Gamma-aminobutyric acid (GABA), $NH_2(CH_3)_3-CO_2H$, is an endogenous substance and is biologically active due to interaction with a specific receptor but is incapable, by itself, of penetrating the encephalic barrier. Accordingly, GABA has been found to be active *in vitro* but relatively inactive *in vivo*. The compounds of the present invention, on the other hand, are active both *in vitro* and *in vivo*. To show this activity of the compounds of the present invention, *in vitro* tests measuring the binding levels of radioactive gamma-aminobutyric acid, ^{3}H-GABA, on synaptic membranes of the rat cortex were carried out according to the method of Enna and Snyder [Enna, S.J. and Snyder, S.H., Mol. Pharmacol. 13, 442-353 (1977)].

Table I, herein after, presents the results of these tests, expressed in percentage of the fixed active product, comparing the *in vitro* activity of Product 1 with the activities of the individual components which comprise Product 1. The results show that sphingosine alone exhibits no biological activity while GAB alone exhibits activity comparable to that of Product 1.

TABLE I

Product 1

Binding on rat cortex membranes

Product utilized	Product	bound %
• ^{3}H-GABA $2.10^{-8}M$		100
• ^{3}H-GABA $2.10^{-8}M$	+ GABA $10^{-8}M$	90
	+ GABA $10^{-7}M$	45
	+ GABA $10^{-6}M$	25
	+ GABA $10^{-5}M$	20
	+ GABA $10^{-4}M$	20
• ^{3}H-GABA $2.10^{-8}M$	+ sphingosine $10^{-8}M$	100
	+ sphingosine $10^{-7}M$	100
	+ sphingosine $10^{-6}M$	100
	+ sphingosine $10^{-5}M$	100
	+ sphingosine $10^{-4}M$	100
• ^{3}H-GABA $2.10^{-8}M$	+ product 1 $10^{-8}M$	95
	+ product 1 $10^{-7}M$	60
	+ product 1 $10^{-6}M$	40
	+ product 1 $10^{-5}M$	25
	+ product 1 $10^{-4}M$	20

TABLE II

Product 1

Anticonvulsivant effects in rat

	Isoniazide 160 mg/kg (s.c.)	Isoniazide 160 mg/Kg (s.c.) + GABA 8 mg/kg (i.p.)	Isoniazide 160 mg/kg (s.c.) + Sphingosine 12 mg/kg (i.p.)	Isoniazide 160 mg/kg (s.c.) + Product 1 20 mg/kg (i.p.)
• Number of animals in convulsions	26/30	24/30	20/30	9/30
• Latency of the convulsions measured in seconds	3070 ± 110	3100 ± 156	3700 ± 200	4500 ± 330
• Number of dead animals	15	14	9	3

b. in vivo tests:

The *in vivo* activity of Product 1 was measured by the method described by Costa et al [E. Costa, A. Guidotti and C. C. Mao; "Evidence for involvement of GABA in the Action of Benzodiazepines: Studies in Rat Cerebellum" in Mechanism of Action of Benzodiazepines; Ed. by E. Costa and P. Greengard, New York, Raven Press. pp. 113-130 (1975)] and by Loescher and Frey [Loesher, W. and Frey, H.H.; "Effect of convulsant and anticonvulsant agents on level and metabolism of gamma-aminobutyric acid in mouse brain"; Naunyn-Schmiedeberg's Arch. Pharmacol. 296, 263-269 (1977)].

These tests are based on the known activity of iosoniazide to cause convulsions and a lowering of the GABA cerebral levels and the glutamic-decarboxylase enzyme activity.

According to the test method, isoniazide is administered to the control animas (rats) while isoniazide and the appropriate test compound are administered to the groups of test animals and the results are measured in terms of the number of animals exhibiting convulsions, the latency of convulsions and the number of deaths.

The results are presented in Table II, herein-above, and show that Product 1 has far superior *in vivo* activity as compared to GABA or sphingosine alone.

Product 3 of Example 3 - Dihydrolysergylsphinsoine amide -

a. in vitro tests:

The *in vitro* biological activity was determined by comparative tests measuring the binding power of the labelled spiroperidole (^{3}H)-spiroperidole on hypophysis sinaptosomal rat membranes according to the method described by Greese et al [Greese I., Schneider R. and Snyder S.H.; "H-spiroperidole labels dopamine receptors in pituitary and brain"; Europ. J. Pharmacol. 46, 377-381 (1977)].

The results obtained and illustrated in Table III, herein-after, show that the binding power of Product 3 is significant and far superior, under the same experimental conditions, to that of dihydrolysergic acid or sphingosine alone.

TABLE III

Product 3

Binding to hypophysis membranes of rat

Product utilized	Product	bound %
• (^{3}H) spiroperidole 2.10^{-9}M *(Control)*		100
• (^{3}H) spiroperidole 2.10^{-9}M + dihydrolysergic acid	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 95 45
• (^{3}H) spiroperidole 2.10^{-9}M + sphingosine	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 100 100
• (^{3}H) spiroperidole 2.10^{-9}M + Product 3	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 90 40 10

TABLE IV

Product 3

Hypoprolactinemic effect in rats

Product utilized		Prolactin ng/ml	Inhibition %
• Control at the circadian peak at 4 p.m.		68.0 ± 5.4	0
• Dihydrolysergic acid :	0.5 mg/kg	60.0 ± 3.2	0
	5.0 mg/kg	51.0 ± 6.7	25
• Sphingosine :	0.5 mg/kg	71.0 ± 4.2	0
	5.0 mg/kg	62.0 ± 6.8	0
• Product 3 :	0.5 mg/kg	38.7 ± 4.7	42
	5.0 mg/kg	32.2 ± 5.7	52
• Control : Sulpiride 10 γ/kg		77.0 ± 9.0	0
• Sulpiride + Dihydrolysergic acid :	0.5 mg/kg	66.0 ± 2.8	0
	5.0 mg/kg	65.0 ± 4.6	0
• Sulpiride + sphingosine :	0.5 mg/kg	72.0 ± 4.5	0
	5.0 mg/kg	77.0 ± 8.7	0
• Sulpiride + Product 3 :	0.5 mg/kg	53.7 ± 8.5	30
	5.0 mg/kg	31.2 ± 2.5	60

b. in vivo tests:

The *in vivo* biological activity of Product 3 was measured by evaluating the serum levels of prolactin in hyperprolactinemic animals according to the RIA method (radioimmunoassay) and the instructions in the NIAMDD program.

The results obtained and illustrated in Table IV, herein-above, expressed as % of inhibition, show that Product 3 exhibits significant biological activity, especially as compared to the weak effect of dihydrolysergic acid.

▪ Product 15 of Example 15 - Dihydrolysergyldihydrosphinsoine amide -

The *in vitro* biological activity and *in vivo* activities of Product 15 were evaluated according to the same methods as used above for Product 3 of Example 3.

The results obtained and presented in Tables V and VI show the *in vitro* and *in vivo* activities of Product 15 to be far superior to either dihydrolysergic acid or dihydrosphingosine alone.

▪ Product 2.2 of Example 2 - Lysergylsphingosine amide -

The *in vitro* and *in vivo* biological activities of Product 2.2 were evaluated according to the same methods as described above for Product 3, Example 3.

The results obtained and presented in Tables VII and VIII show the *in vitro* and *in vivo* activities of Product 2.2 to be far superior to either lysergic acid or sphingosine alone.

▪ Product 16 of Example 16 - Dihydrolisergylpsychosine amide -

The *in vitro* and *in vivo* biological activities of Product 16 were evaluated according to the same methods as described for Product 3, Example 3.

The results obtained and presented in Tables IX and X show that *in vitro* and *in vivo* activities of Product 16 to be far superior to either dihydrolysergic acid or psychosine alone.

TABLE V

Product 15

Binding to hypophysis membranes of rat

Product utilized	Product	bound %
• (^{3}H) spiroperidole 2 nM *(Control)*		100
• (^{3}H) spiroperidole 2 nM + dihydrolysergic acid	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 95 45
• (^{3}H) spiroperidole 2 nM + dihydrosphingosine	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 100 100
• (^{3}H) spiro peridole 2 nM + Product 15	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 90 30 20

TABLE VI

Product 15

Hypoprolactinemic effect in rats

Product utilized	Prolactin ng/ml	Inhibition %
• Control at the circadian peak at 4 p.m.	62.0 ± 3.8	
• Dihydrolysergic acid : 0.5 mg/kg	60.0 ± 4.1	0
5.0 mg/kg	48.0 ± 5.1	0
• Dihydrosphingosine : 0.5 mg/kg	66.0 ± 4.2	23
5.0 mg/kg	60.0 ± 2.8	0
• Product 15 : 0.5 mg/kg	40.0 ± 5.6	0
5.0 mg/kg	31.0 ± 3.4	35
• Control : Sulpiride 10 γ/kg	85.0 ± 9.0	50
• Sulpiride + Dihydrolysergic acid : 10 γ/kg + 0.5 mg/kg	77.0 ± 5.0	0
10 γ/kg + 5.0 mg/kg	76.0 ± 8.0	0
• Sulpiride + Dihydrosphingosine : 10 γ/kg + 0.5 mg/kg	81.0 ±11.0	0
10 γ/kg + 5.0 mg/kg	74.0 ± 6.0	0
• Sulpiride / product 15 : 10 γ/kg + 0.5 mg/kg	48.0 ± 4.0	44
10 γ/kg + 5.0 mg/kg	39.0 ± 6.0	55

TABLE VII

Product 2.2

Binding to hypophysis membranes of rat

Product utilized	Product	bound %
• (^{3}H) spiroperidole 2 nM *(Control)*		100
• (^{3}H) spiroperidole 2 nM + lysergic acid	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 90 60
• (^{3}H) spiroperidole 2 hM + sphingosine	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 100 100
• (^{3}H) spiroperidole 2 nM + Product 2.2	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 85 55 35

TABLE VIII

Product 2.2

Hypoprolactinemic effect in rats

Product utilized		Prolactin ng/ml	Inhibition %
• Control at the circadian peak at 4 p.m.		65.0 ± 4.8	0
• Lysergic acid :	0.5 mg/kg	61.0 ± 3.8	0
	5.0 mg/kg	52.0 ± 6.2	20
• Sphingosine :	0.5 mg/kg	68.0 ± 6.0	0
	5.0 mg/kg	61.0 ± 8.0	0
• Product 2.2 :	0.5 mg/kg	48.0 ± 4.8	27
	5.0 mg/kg	40.0 ± 2.6	39
• Control : Sulpiride 10 γ/kg		87.0 ± 8.7	0
• Sulpiride + Lysergic acid :			
	10 γ/kg + 0.5 mg/kg	76.0 ± 9.0	13
	10 γ/kg + 5.0 mg/kg	73.0 ±10.0	16
• Sulpiride + Sphingosine :			
	10 γ/kg + 0.5 mg/kg	81.0 ±11.0	0
	10 γ/kg + 5.0 mg/kg	74.0 ± 6.0	14
• Sulpiride + Product 2.2 :			
	10 γ/kg + 0.5 mg/kg	59.0 ± 6.0	32
	10 γ/kg + 5.0 mg/kg	49.0 ± 5.0	44

TABLE IX

Product 16

Binding to hypophysis membranes of rat

Product utilized	Product	bound %
• (^{3}H) spiroperidole 2 nM *(Control)*		100
• (^{3}H) spiroperidole 2 nM + dihydrolysergic acid	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 90 60
• (^{3}H) spiroperidole 2 nM + psychosine	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 100 90 60
• (^{3}H) spiroperidole 2 nM + Product 16	10^{-7}M 10^{-6}M 10^{-5}M 10^{-4}M	100 80 45 25

TABLE X

Product 16

Hypoprolactinemic effect in rats

Product utilized		Prolactin ng/ml	Inhibition %
• Control at the circadian peak at 4 p.m.		58.0 ± 6.0	0
• Dihydrolysergic acid :	0.5 mg/kg	57.0 ± 5.0	0
	5.0 mg/kg	49.0 ± 6.0	16
• Psychosine :	0.5 mg/kg	50.0 ± 5.0	14
	5.0 mg/kg	41.0 ± 5.0	30
• Product 16 :	0.5 mg/kg	40.0 ± 7.0	31
	5.0 mg/kg	31.0 ± 6.0	47
• Control : Sulpiride 10 γ/kg		81.0 ± 9.0	0
• Sulpiride + Dihydrolysergic acid :			
	10 γ/kg + 0.5 mg/kg	77.0 ± 6.0	0
	10 γ/kg + 5.0 mg/kg	70.0 ± 4.0	14
• Sulpiride + psychosine :			
	10 γ/kg + 0.5 mg/kg	70.0 ± 6.0	14
	10 γ/kg + 5.0 mg/kg	61.0 ± 7.0	25
• Sulpiride + Product 16 :			
	10 γ/kg + 0.5 mg/kg	51.0 ± 7.0	37
	10 γ/kg + 5.0 mg/kg	39.0 ± 4.0	52

THERAPEUTIC USES.

According to the present invention, the organic amides derived from nitrogenous lipids can be used as medicaments for various therapeutic uses, in particular for those uses corresponding to the activities of the active acids from which the amides are prepared.
For example, derivatives of lysergic, isolysergic, dihydrolysergic, 2-bromo-lysergic, 2-bromo-dihydrolysergic, 1-methyl-lysergic, 1-methyl-dihydrolysergic, 1-methyl-2-bromo-lysergic, 1-methyl-2-bromo-dihydrolysergic, gamma-amino-butyric, valproic, trimethoxybenzoic and nicotinic acid are suitable for use as medicaments capable of exhibiting pharmacological activity on the central nervous system.
The derivatives of lysergic acid, 2-bromo-lysergic, 1-methyl-lysergic and 1-methyl-2-bromo-lysergic also exert a significant activity on the uterus.
Specifically, the compounds of the present invention which are experimentally active against isoniazid convulsions and on the binding of GABA *in vitro*, and the pharmaceutical compositions containing them, may be therapeutically useful in pathologies connected with changes in the function of the GABAurgic system, since these products are able to enhance levels of GABA in the central nervous system (CNS) and in the specific cerebral areas, thereby enabling the GABA, bound to natural amino-alcohols, to penetrate the blood-brain barrier.
To be more precise, these compounds and the pharmaceutical preparations containing them may be usefully employed in the prevention of convulsive states which usually give rise to tonoclonic contractions and/or loss of consciousness, as in epilepsy; that is, in focal epilepsy, in psychomotorial epilepsy, in major epilepsy, in idiopathic epilepsy, in status epilipticus and in centroencephalic epilepsy (in minor epilepsy, akinetic attacks, mioclonic epilepsy) and in general, in pathologies deriving from decrease of inhibitoru control in the CNS.

The compounds which have proved to be active in inhibiting the serum levels of prolactin and in the blinding *in vitro* of the dopaminergic ligand in the hypophysis, and the pharmaceutical compositions deriving from them, as exemplified in the *in vivo* and *in vitro* data noted above, may be usefully employed in pathologies which present alterations in the release of neuropeptides from hypophysis as prolactin due to changes in the regulation of the neurotransmittor systems with loss of dopaminergic

system tonic inhibition or, in general, of the hypothalamic routes as in hyperprolactinemias caused by neuroleptics such as sulpiride chlorpromazine, etc.

Thus, the drugs deriving from the compounds of the present invention may be used in the treatment of behavioral alterations resulting from modifications of neuropeptide hormones from hypophysis as hyperprolactinemic syndromes with loss of lipids and impotence, and hypopituitarism with changes in personality, apathy, indifference, astenia, loss of lipido and confusion, and premenstrual syndromes with depression and changes of mood and climacteric syndromes with variations in mood, irritability, anxiety, nervousness and depression.

The compounds of the present invention can be administered as pharmaceutical compositions containing, as an active ingredient, one or more of the amides in association with one or more compatible and pharmaceutically acceptable excipients. The compositions can be administered via various administration routes, such as injectable solutions, tablets, gelatine capsules and suppositories. The dosage administered will vary depending upon the desired effect and administration route, but, for example, in oral administration the dosages can be between 10 and 300 mg of active substance per day with a single dosage of from 10 to 100 mg.

The following are examples of pharmaceutical compositions for oral administration:

a. Pharmaceutical preparation 1:
10 mg tablets
Each tablet contains:

— Active substance	10 mg
— Microcrystalline cellulose	100 mg
— Lactose	150 mg
— Magnesium stearate	2.5 mg
— Starch	20 mg

b. Pharmaceutical preparation 2:
50 mg tablets
Each tablet contains:

— Active substance	50 mg
— Microcrystalline cellulose	100 mg
— Lactose	110 mg
— Magnesium stearate	2.5 mg
— Starch	20 mg

c. Pharmaceutical preparation 3:

100 mg tablets

Each tablet contains:

— Active substance	100 mg
— Microcrystalline cellulose	100 mg
— Lactose	2.5 mg
— Magnesium stearate	3.5 mg
— Starch	25 mg

d. Pharmaceutical preparation 4:

10 mg gelatine capsule

Each capsule contains:

— Active substance	10 mg
— Vegetable oil	100 mg
— Gelatine	100 mg
— Glycerine	25 mg

e. Pharmaceutical preparation 5:

50 mg gelatine capsule

Each capsule contains:

— Active substance	50 mg
— Vegetable oil	120 mg
— Gelatine	110 mg
— Glycerine	30 mg

f. Pharmaceutical preparation 6:

100 mg gelatine capsule

Each capsule contains:

— Active substance	100 mg
— Vegetable oil	150 mg
— Gelatine	130 mg
— Glycerine	44 mg

WE CLAIM

1.- Organic amide compounds of the formula:

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3$$

wherein:

R_1-CO is a residue of a carboxylic acid with the proviso that the carboxilic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids;

R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and

R_3-N is a residue of a nitrogenous lipid,

or pharmaceutically acceptable salts thereof

2.- Compounds according to claim 1, wherein said carboxylic acid is selected from the group consisting of lysergic, isolysergic, dihydrolysergic, 2-bromolysergic, 2-bromo-dihydrolysergic, 1-methyllysergic, 1-methyl-dihydrolysergic, 1-methyl-2-bromo-lysergic, 1-methyl-2-bromo-dihydrolysergic, gamma-aminobutyric, valproic, trimethoxybenzoic, nicotinic, isonicotinic, picolinic and theophyllineacetic acids.

3.- Compounds according to claim 2, wherein:

R_2 represents a hydrogen atom.

4.- Compounds according to claim 1 or 2, wherein said nitrogenous lipid is a phospholipid.

5.- Compounds according to claim 1 or 2, wherein said nitrogenous lipid is a sphingolipid.

6.- Compounds according to claim 4, wherein said phospholipid is a phosphatidylethanolamine or a phosphatidylserine.

7.- Compounds according to claim 5, wherein said sphingolipid is a sphingolipid having a free amine (NH_2) group and a residue of sphingosine having from 12 to 22 carbon atoms.

8.- Compounds according to claim 5,wherein said sphingolipid is selected from the group consisting of sphingosine, dihydrosphingosine, psychosine, dihydropsychosine, sphingosinephosphorylcholine, dihydro-sphingosinephosphorylcholine and phytosphingosine.

9.- Compounds according to claim 1, wherein:

R_2 is hydrogen,

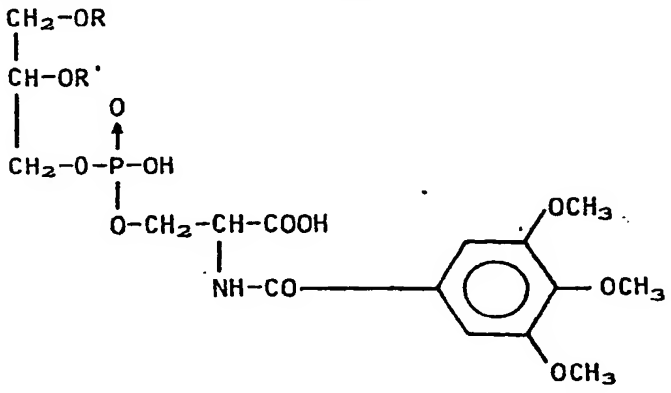
said lipid is sphingosine, and
said carboxylic acid is selected from the group consisting of gamma-amino-butyric acid, lysergic acid, isolysergic acid, dihydrolysergic acid, valproic acid, trimethoxybenzoic acid, theophyllineacetic acid, nicotinic acid and isonicotinic acid.

10.- Compounds according to claim 1, wherein:
R_2 is hydrogen,
said lipid is psychosine, and
said carboxylic acid is selected from the group consisting of trimethoxy-benzoic, nicotinic acid, dihydrolysergic acid, lysergic acid and isolysergic acid.

11.- Compounds according to claim 1, wherein:
R_2 is hydrogen,
said lipid is sphingosinephosphorylcholine, and
said carboxylic acid is trimethoxybenzoic acid.

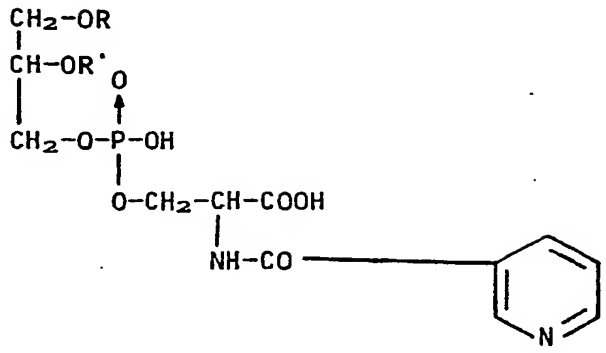
12.- Compounds according to claim 1, wherein:
R_2 is hydrogen,
said lipid is dihydrosphingosine, and
said carboxylic acid is dihydrolysergic acid.

13.- Compounds according to claim 1, which are trimethoxybenzoyl-phosphatidylserine amides of the formula:



wherein:
R and R' are saturated or unsaturated fatty acids.

14.- Compounds according to claim 1, which are nicotinylphosphatidylserine amides of the formula:



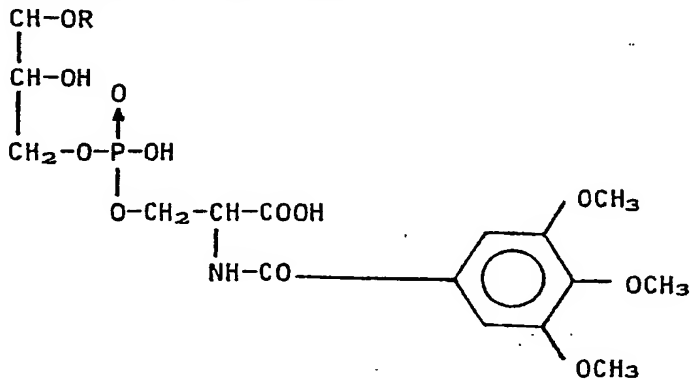
wherein:

R and R' are saturated or unsaturated fatty acids.

15.- Compounds according to claim 13 or 14, wherein:

said R' is selected from the group consisting of stearic, palmitic, oleic, linolenic, linoleic and arachidonic acids.

16.- Compounds according to claim 1, which are trimethoxybenzoyl-isophosphatidylserine amides of the formula:



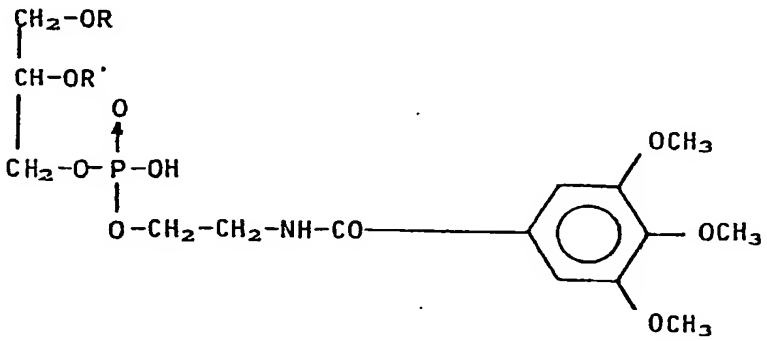
wherein:

R is a saturated or unsaturated fatty acid.

17.- A compound according to claim 16, wherein:

R is stearic or oleic acid.

18.- Compounds according to claim 1, which are trimethoxybenzoyl-phosphatidylethanolamine amides of the formula:



wherein:

R and R' are saturated or unsaturated fatty acids.

19.- Compounds according to claim 18, wherein:
R and R' are selected from the group consisting of oleic, stearic, palmitic, linoleic and arachidonic acids.

20.- A pharmaceutical composition containing as an active ingredient an organic amide compound of the formula:

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3$$

wherein:
R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,
R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and
R_3-N is a residue of a nitrogenous lipid,
or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier ou diluent.

21.- A pharmaceutical composition according to claim 20, wherein: said carboxylic acid is selected from the group consisting of lysergic, isolysergic, dihydrolysergic, 2-bromo-lysergic, 3-bromo-dihydrolysergic, 1-methyl-lysergic, 1-methyl-dihydrolysergic, 1-methyl-2-bromo-lysergic, 1-methyl-2-bromo-dihydrolysergic, gamma-amino-butyric, valprioc, trimethoxybenzoic, nicotinic, isonicotinic, picolinic and theophylline-acetic acids.

22.- A pharmaceutical composition according to claim 20, wherein:
R_2 represents a hydrogen atom.

23.- A pharmaceutical composition according to claim 20, wherein: said nitrogenous lipid is a phospholipid.

24.- A pharmaceutical composition according to claim 20, wherein: said nitrogenous lipid is a sphingolipid.

25.- A pharmaceutical composition according to claim 23, wherein: said phospholipid is a phosphatidyl-ethanolamine or a phosphatidylserine.

26.- A pharmaceutical composition according to claim 24, wherein: said sphingolipid is a sphingolipid having a free amine (NH_2) group and a residue of sphingosine from 12 to 22 carbon atoms.

27.- A pharmaceutical composition according to claim 20, wherein: said sphingolipid is selected from the group consisting of sphingosine, dihydrosphingosine, psychosine, dihydropsychosine, sphingosinephosphoryl-choline, dihydrosphingosine, phosphorylcholine and phytosphingosine.

28.- A pharmaceutical composition according to claim 20, wherein:
R_2 is hydrogen,
said lipid is sphingosine, and
said carboxylic acid is selected from the group consisting of gamma-amino-butyric acid, lysergic acid, isolysergic acid, dihydrolysergic acid, valproic acid, trimethoxybenzoic acid, theophylline-acetic acid, nicotinic acid and isonicotinic acid.

29.- A pharmaceutical composition according to claim 20, wherein:
R_2 is hydrogen,
said lipid is psychosine, and
said carboxylic acid is selected from the group consisting of trimethoxy-benzoic acid, nicotinic acid, dihydrolysergic acid, lysergic acid and isolysergic acid.

30.- A pharmaceutical composition according to claim 20, wherein:
R_2 is hydrogen,
said lipid is sphingosinephosphorylcholine, and
said carboxylic acid is trimethoxybenzoic acid.

31.- A pharmaceutical composition according to claim 20, wherein:
R_2 is hydrogen,
said lipid is dihydrosphingosine, and
said carboxylic acid is dihydrolysergic acid.

32.- A process for preparing organic amide compounds of the formula:

$$R_1-CO-\underset{\displaystyle R_2}{\underset{|}{N}}-R_3$$

wherein:
R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,
R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and
R_3-N is a residue of a nitrogenous lipid,
the process comprising the steps of:
a) reacting a carboxylic acid of the formula R_1COOH with a phenol to form an ester; and
b) reacting said ester with said nitrogenous lipid.

33.- The process according to claim 32, wherein:
said phenol is para-nitrophenol.

34.- A process for preparing organic amide compounds of the formula:

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3$$

wherein:

R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,

R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and

R_3-N is a residue of a nitrogenous lipid,

the process comprising the steps of:

a) reacting a carboxylic acid of the formula R_1-COOH with trifluoroacetic acid to form a mixed anhydride; and

b) reacting said mixed anhydride with said nitrogenous lipid.

35.- A process for preparing organic amide compounds of the formula:

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3$$

wherein:

R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,

R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and

R_3-N is a residue of a nitrogenous lipid,

the process comprising reacting a carboxylic acid of the formula R_1-COOH with said nitrogenous lipid in the presence of at least one member selected from the group consisting of a carbociimide and 1-hydrobenzotriazol.

36.- The process according to claim 35, wherein:
said carbodiimide is dicyclohexylcarbodiimide, benzylisopropylcarbodiimide or benzylethylcarbodiimide.

37.- A process for preparing organic amide compounds of the formula:

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3$$

wherein:

R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,

R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and

R_3-N is a residue of a nitrogenous lipid,

the process comprising the steps of:

a) preparing the chloride of a carboxylic acid of the formula R_1-COOH; and

b) reacting said chloride with said nitrogenous lipid.

38.- A process for preparing organic amide compounds of the formula:

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3$$

wherein:

R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,

R is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and

R_3-N is a residue of a nitrogenous lipid,

the process comprising the steps of:

a) reacting a carboxylic acid of the formula R_1-COOH with N,N'-carbonyldiimidazol to form an acylimidazol thereof; and

b) reacting said acylimidazol with said nitrogenous lipid.

39.- A process for preparing organic amide compounds of the formula:

$$R_1\text{-}CO\text{-}N(R_2)\text{-}R_3$$

wherein:

R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,

R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and

R_3-N is a residue of a nitrogenous lipid,

the process comprising the steps of:

a) reacting gamma-aminobutyric acid with a protecting group to thereby protect the amine group thereof;

b) reacting said protected gamma-aminobutyric acid with said nitrotenous lipid according to any one of claims 32-38; and

c) subsequently removing said protecting group.

40.- The process according to claim 39, wherein:
said protecting group is a phthaloyl or benzyloxy carbonyl.

41.- A method for increasing or stimulating the *in vivo* biological activity of *in vitro* biologically active carboxylic acids which comprises preparing an amide of said carboxylic acid with a nitrogenous lipid to forme a compound of the formula:

$$R_1\text{-}CO\text{-}\underset{\displaystyle R_2}{\underset{|}{N}}\text{-}R_3$$

wherein:
R_1-CO is a residue of a carboxylic acid with the proviso that the carboxylic acid is not a natural fatty acid normally bound to nitrogen of nitrogenous lipids,
R_2 is a hydrogen atom, a saturated C_{1-7} alkyl group or a saturated C_{4-7} cycloalkyl group, and
R_3-N is a residue of a nitrogenous lipid,
or pharmaceutically acceptable salts thereof.

42.- A method according to claim 41, wherein:
said carboxylic acid is selected from the group consisting of lysergic, isolysergic, dihydrolysergic, 2-bromolysergic, 2-bromo-dihydrolysergic, 1-methyllysergic, 1-methyl-dihydrolysergic, 1-methyl-2-bromo-lysergic, 1-methyl-2-bromo-dihydrolysergic, gamma-aminobutyric, valproic, trimethoxybenzoic, nicotinic, isonicotinic, picolinic and theophylline-acetic acids.

43.- A method according to claim 41, wherein:
R_2 represents a hydrogen atom.

44.- A method according to claim 41 or 42, wherein:
said nitrogenous lipid is a phospholipid.

45.- A method according to claim 41 or 42, wherein:
said nitrogenous lipid is a sphingolipid.

46.- A method according to claim 44, wherein:
said phospholipid is a phosphatidylethanolamine or a phosphatidylserine.

47.- A method according to claim 45, wherein:
said sphingolipid is selected from the group consisting of sphingosine, dihydrosphingosine, psychosine, dihydropsychosine, sphingosinephosphorylcholine, dihydrosphingosinephosphorylcholine and phytosphingosine.

48.- A method according to claim 41, wherein:
R_2 is hydrogen,
said lipid is sphingosine, and
said carboxylic acid is selected from the group consisting of gamma-aminobutyric acid, lysergic acid, isolysergic acid, dihydrolysergic acid, valproic acid, trimethoxybenzoic acid, theophyllineacetic acid, nicotinic acid and isonicotinic acid.

49.- A method according to claim 41, wherein:
R_2 is hydrogen,
said lipid is psychosine, and
said carboxylic acid is selected from the group consisting of trimethoxybenzoic acid, nicotinic acid, dihydrolysergic acid, lysergic acid and isolysergic acid.

50.- A method according to claim 41, wherein:
R_2 is hydrogen,
said lipid is sphingosinephosphorylcholine, and
said carboxylic acid is trimethoxybenzoic acid.

51.- A method according to claim 41, wherein:
R_2 is hydrogen,
said lipid is dihydrosphingosine, and
said carboxylic acid is dihydrolysergic acid.

European Patent Office

EUROPEAN SEARCH REPORT

0072286

EP 82 40 1384

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
X	CHEMICAL ABSTRACTS, vol. 65, no. 2, 18th July 1966, column 2079d,e, Columbus, Ohio, USA A.YA. VEINBERG et al.: "Sphingosine and its natural compounds. V. Mechanism of conversion of threo-trans-1-hydroxy-2-benzamido-3-chloro-4-octadecene into the hydrochloride of erythro-3-O-benzoylsphingosine" & ZH. ORGAN. KHIM. 2(2), 337-340, 1966 * Abstract *	1	C 07 H 15/18 C 07 H 15/26 C 07 F 9/09 C 07 F 9/10 C 07 F 9/58 C 07 D 457/06 C 07 D 473/08 C 07 D 213/82 C 07 D 213/81 C 07 C 103/50 C 07 C 103/38 C 07 C 103/78 A 61 K 37/00
X	CHEMICAL ABSTRACTS, vol. 62, no. 13, 21st June 1965, column 16801d, Columbus, Ohio, USA TAMOTSU TAKETOMI et al.: "Physiological activity of psychosine" & JAPAN. J. EXPTL. MED. 34(5), 255-265, 1964 * Abstract *	1	
X	CHEMICAL ABSTRACTS, vol. 70, no. 1, 6th January 1969, page 163, no. 1835h, Columbus, Ohio, USA T. TAKETOMI et al.: "Immunochemical studies of lipids. II. Antigenic properties of synthetic sphingosylphosphorylcholine-protein conjugate" & JAP. J. EXP. MED. 1967, 37(5), 423-432 * Abstract *	1	TECHNICAL FIELDS SEARCHED (Int. Cl. ³) C 07 H 15/00 C 07 F 9/00 C 07 D 457/00 C 07 D 473/00 C 07 D 213/00 C 07 C 103/00

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	08-11-1982	BESLIER L.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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D : document cited in the application
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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
X	CHEMICAL ABSTRACTS, vol. 64, no. 11, 23rd May 1966, column 16449c, Columbus, Ohio, USA TAMOTSU TAKETOMI et al.: "Antigen properties of a synthetic protein complex with glycolipids and related substances" & LIPIDS 1(1), 31-40, 1966 * Abstract *	1	
A	FR-A-1 200 951 (CIBA) * Complete specification *	1	
X	FR-A-1 230 430 (CIBA) * Complete specification *	1	
A	US-A-4 005 089 (MAGO NEE KARACSONY) * Complete specification *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	08-11-1982	BESLIER L.M.

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